BIRTH DEFECT RISK FACTOR SERIES: HOLOPROSENCEPHALY

DEFINITION

Holoprosencephaly is characterized by the failure of the forebrain (the front portion of the brain or prosencephalon) to divide completely into right and left hemispheres. There is tremendous variation in the severity of this defect. In alobar holoprosencephaly, there is a single, small ventricular cerebrum without division into hemispheres. There is a single ventricle, and absent olfactory bulbs and optic tracts. In semilobar holoprosencephaly, there are rudimentary cerebral lobes with partially separated hemispheres. In lobar holoprosencephaly, the central lobes are well developed and the fissure between the hemispheres is distinct; however, there is still some fusion of brain structures. Facial anomalies are frequently present, ranging in severity from a flattened nose and closely-spaced eyes through a cleft or split lip and a single nostril to cyclopia, where a nose-like proboscis is present over a single eye in the middle of the face. Hydrocephaly or microcephaly are sometimes present. Approximately half of all infants or fetuses with holoprosencephaly also have chromosomal abnormalities, most often trisomy 13 (Blaas et al., 2002; Bullen et al., 2001; Ming and Muenke, 1998; Peebles, 1998; Olsen et al., 1997; Croen et al., 1996; Rasmussen et al., 1996; Cohen, 1989). Certain genes or chromosomal regions have been linked to holoprosencephaly; among the genes is *Sonic Hedgehog (SHH)* found in the 7q36 region (Ming and Muenke, 1998; Peebles, 1998), *SIX3* (Wallis et al., 1999), and *ZIC2* (Brown et al., 2001; Brown et al., 1998). The incidence is much higher among fetal deaths than among live births (Odent et al., 1998).

Prenatal ultrasound can detect the more severe forms of holoprosencephaly, and associated defects such as hydrocephaly and chromosomal abnormalities (Peebles, 1998; Vintzileos; 1987; Chervenak et al., 1985; Chervenak et al., 1984). Studies from various birth defects surveillance systems have found that, in regions where elective termination is allowed, prenatal diagnosis and elective termination reduce the birth prevalence of holoprosencephaly (Blaas et al., 2002; Bullen et al., 2001; Forrester and Merz, 2000; Croen et al., 1996; Rasmussen et al., 1996).

EMBRYOLOGY

Holoprosencephaly occurs as a result of failure of the forebrain (prosencephalon) of the embryo to divide into the two cerebral hemispheres, which normally occurs by the 5th-6th week gestation.

DEMOGRAPHIC AND REPRODUCTIVE FACTORS

Studies have reported differences in risk between **racial/ethnic groups**, but the differences have not been consistent between the studies (Forrester and Merz, 2000; Olsen et al., 1997; Croen et al., 1996; Rasmussen et al., 1996).

Several studies have reported an increase in holoprosencephaly prevalence over time. However, these **secular trends** may reflect improvements in the diagnosis and ascertainment of cases (Rasmussen et al., 1996).

One investigation that evaluated **geography** failed to find differences in risk between urban and rural areas (Forrester and Merz, 2000).

Maternal age has been associated with holoprosencephaly risk. Women younger than age 25 and older than age 35 are more likely to have an infant with holoprosencephaly. The increased risk among older women results from the fact that older women are more likely to have an infant with a chromosomal abnormality (Forrester and Merz, 2000; Olsen et al., 1997; Croen et al., 1996; Rasmussen et al., 1996).

The **recurrence risk** for a woman who has had one child with holoprosencephaly depends on whether a chromosomal abnormality is involved and the type of chromosomal abnormality. Multiple occurrences of

isolated holoprosencephaly without chromosomal abnormalities have been reported in the same family, further supporting a genetic or hereditary basis for at least a portion of holoprosencephaly cases (Ming and Muenke, 1998; Odent et al., 1998; Peebles, 1998; Rasmussen et al., 1996).

Infant sex influences the risk for holoprosencephaly. The defect is much more common among females than among males (Croen et al., 2000; Forrester and Merz, 2000; Olsen et al., 1997; Croen et al., 1996; Rasmussen et al., 1996), although one study observed a higher rate of males among prenatally diagnosed cases (Blaas et al., 2002). One investigation reported a higher than anticipated number of holoprosencephaly cases among **multiple births** (Bullen et al., 2001).

One investigation reported no statistically significant association between holoprosencephaly and **macrosomia** (Waller et al., 2001).

FACTORS IN LIFESTYLE OR ENVIRONMENT

One study has reported an association between low **socioeconomic status** and holoprosencephaly risk (Cohen, 1989). However, this observation has not been confirmed.

A case-control study found a suggestion of an association between cytogenetically normal holoprosencephaly and maternal **alcohol**, **smoking**, **respiratory illness medications**, and **salicylate-containing medications** (Croen et al., 2000). However, some of these associations were not statistically significant. Another study reported no significant link between alcohol, smoking, or **x-ray** exposure and holoprosencephaly risk (Cohen, 1989). An investigation failed to identify any significant association between holoprosencephaly and proximity to various types of **industry** (Castilla et al., 2000).

Maternal **diabetes** has been reported by several studies to increase holoprosencephaly risk (Croen et al., 2000; Ming and Muenke, 1998; Peebles, 1998; Ramos-Arroyo et al., 1992). However, one investigation reported no relationship between diabetes and holoprosencephaly (Becerra et al., 1990). Other maternal factors that have been tentatively associated with holoprosencephaly, based on anecdotal evidence or studies involving small numbers of cases, include **retinoic acid**, **salicylates**, **estrogen/progestin**, **anticonvulsants**, **weight reduction diets**, **previous pregnancy loss**, and **congenital infection** with **cytomegalovirus**, **rubella**, **and toxoplasmosis** (Croen et al., 1996). One survey that involved a small number of cases failed to identify any association between holoprosencephaly and retinoic acid (De Wals et al., 1991). A case-control study suggests that risk of holoprosencephaly may be increased with maternal use of **misoprostol**, a synthetic prostaglandin used for elective termination (Orioli and Castilla, 2000).

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Please Note: *The primary purpose of this report is to provide background necessary for conducting cluster investigations. It summarizes literature about risk factors associated with this defect. The strengths and limitations of each reference were not critically examined prior to inclusion in this report. Consumers and professionals using this information are advised to consult the references given for more in-depth information.*

This report is for information purposes only and is not intended to diagnose, cure, mitigate, treat, or prevent disease or other conditions and is not intended to provide a determination or assessment of the state of health. Individuals affected by this condition should consult their physician and when appropriate, seek genetic counseling.